Treatment of Endotoxic Shock

The Dilemma of Vasopressor and Vasodilator Therapy

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• **Hemodynamic studies have demonstrated that the fall of blood pressure in shock caused by endotoxin in dogs does not result primarily from dilatation or "vasomotor collapse." Indeed, vasoconstriction is increased and may be excessive. Progression of shock has recently been blamed on such excessive vasoconstriction. For this reason the use of sympathomimetic drugs as vasopressor agents has been challenged and sympatholytic or adrenolytic agents have been recommended.**

In the present study, vasopressor and vasodilator drugs were used for the treatment of shock in dogs caused by endotoxin. Vasodilator drugs, when used after the onset of shock, hastened a fatal outcome but vasopressor agents were not detrimental when used in moderate doses.

The effectiveness of the vasopressor agent is not necessarily due to a primary vasoconstrictor action on arteries and arterioles, as previously assumed.

THE TERM *shock* is descriptive of a clinical sequence of events, the physiological causes of which are as yet only partially understood. Shock is most often due to loss of blood or other fluid, through injury or following an operation. Prompt replacement of blood or plasma generally restores normal circulation, but in some patients an "irreversible" state of shock develops in spite of adequate fluid replacement. In other instances shock occurs without previous loss of fluid, as in myocardial infarction, in the course of an acute overwhelming infection, as a hypersensitivity (anaphylactic) reaction or after injury to the nervous system. A fall in arterial blood pressure is a characteristic although not an inevitable manifestation of shock regardless of cause. However, the primary defect of shock is not so much a failure to maintain pressure as it is a failure to maintain flow of blood.

The adequacy of blood circulation depends on three basic components: An effective pump, an adequate volume of fluid and a proper capacity of the container. In cardiogenic shock, the pump is at fault. There is uniform agreement as to the importance of supporting the heart by taking measures to maintain effective coronary circulation. In hypovolemic shock, the need for prompt replacement of fluid is generally recognized. Little agreement exists, however, as to the proper therapy in cases in which shock is due to alterations in the capacity of blood vessels. Included in this group are bacteremic (endotoxic) shock, shock states due to hypersensitivity, neurogenic shock and protracted hypovolemic shock which has become refractory to fluid replacement.

Until recently, the cause of shock in this third group was attributed to "generalized vasomotor collapse," implying that the blood circulated sluggishly in paralyzed, distended vessels. Physiological measurements and microscopic observations of blood vessels *in vivo* during shock have indicated, however, that in most cases quite the opposite is true. In experimental animals it was observed that what occurred was excessive vasomotor activity with decided constriction of the arteries and arterioles.[1,6,11]

Sympathomimetic drugs like norepinephrine (Levophed®) and metaraminol (Aramine®) have gained wide acceptance in the effort to counteract hypotension. With a rising blood pressure the patient's general appearance improves, lethargy often gives way to a more alert state of awareness, the critically reduced urine output may be increased and the pulse adjusts to a slower rate and fuller volume. Thus the manifestations of shock are seemingly reversed by the administration of norepinephrine or metaraminol.

Yet vasopressor amines produce their effect at least in part because of their constrictive action on arterioles, thereby elevating arterial pressure. The possibility arises that the additional constriction of an already narrow vascular bed by means of vasopressor drugs may ultimately be injurious and outweigh the beneficial symptomatic effects of the

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Presented at the 90th Annual Meeting of the California Medical Association, Los Angeles, April 30 to May 3, 1961.

Supported by grants-in-aid from the American Heart Association and the Los Angeles County Heart Association, and by Research Grant No. H-5570, National Heart Institute, United States Public Health Service.

treatment. Perhaps drugs that would produce dilatation of arterioles might provide more rational therapy.

The purpose of this report is to summarize experimental studies on the effect of vasopressor and vasodilator drugs on bacterial shock.

MECHANISM OF ENDOTOXIN SHOCK

When endotoxin from Gram-negative bacteria was injected intravenously into dogs, a sharp decline in arterial pressure was observed within 30 seconds while simultaneously the portal vein pressure was decidedly increased. This rise of portal vein pressure and fall in arterial pressure did not reflect acute cardiac failure, for the pressure in the inferior vena cava and systemic veins remained normal or declined slightly. In experiments performed at the University of Minnesota[8] the cardiac output decreased sharply in close association with the fall of arterial pressure. Moderate elevation of peripheral resistance was observed. This would indicate that shock was not due to vasomotor collapse—indeed, quite the opposite was true: The arterial bed became vasoconstricted, at least during the early period of shock.

In a series of experiments performed by one of us in association with MacLean[4] it was demonstrated in dogs that the fall in blood pressure, the decline in cardiac output and the rise in portal vein pressure were due to pooling of large amounts of blood in the splanchnic venous bed. Initially, blood was sequestrated in the liver and when the liver had filled, pooling extended to the submucosal veins of the intestine. These hemodynamic changes were corroborated at autopsy.

The amount of blood pooled was quantitated in two ways. First a system was devised by which, at laparotomy, the liver or a portion of the intestine could be mobilized and weighed in living dogs without interfering with its blood supply. Studies with this technique showed that with onset of shock initially the weight of the liver and subsequently the weight of the intestine increased decidedly.[5]

An experimental method was then devised in association with MacLean, Visscher, and Spink to provide continuous measurements of the amount of blood returned to the heart. The results of these experiments demonstrated that when portal vein pressure was elevated and intestinal blood volume increased, pronounced reduction of venous return consistently occurred.[8] Thus, the initial fall in cardiac output in dogs was clearly related to the removal of blood from active circulation and its storage in the splanchnic venous bed.

HEMODYNAMIC EFFECTS OF VASOPRESSOR AGENT

Experiments were then carried out to determine the effect of metaraminol on the pooling of blood. When metaraminol was administered, the previously stagnant blood in the splanchnic bed was mobilized, thereby increasing venous return and cardiac output. This effect of the vasopressor agent was observed after injection of doses which produced only minimal vasoconstriction.[9] It was concluded that vasopressor agents reverse splanchnic pooling and increase venous return, an effect which directly counteracts the mechanism of endotoxin shock.

VASOPRESSOR AND VASODILATOR THERAPY

The possibility still existed that arteriolar spasm and capillary injury occurring during the later stages of shock might actually be intensified by the use of metaraminol. If this were the case, drugs with sympatholytic or adrenergic blocking action would improve survival.

The effects of vasopressor agents, adrenergic blocking agents, and corticosteroid hormones on the outcome of shock produced by endotoxin were recently evaluated by Lillehei and MacLean.[2,3] In their studies on dogs, vasopressor agents were injected *before* or *coincident with* endotoxin, thereby preventing the blood pressure fall caused by the bacterial toxin. Dibenzyline, chlorpromazine and hydrocortisone were administered one-half day to five days before the induction of shock. Under these experimental conditions, vasopressor agents and particularly metaraminol hastened the fatal outcome, whereas adrenergic blocking drugs and corticosteroid hormones protected against the deleterious effects of the endotoxin.

Similar experiments were repeated in our laboratory, except that the therapeutic agent was administered 15 minutes *after* shock had occurred.

Single intravenous injections of dibenzyline (25 mg. per kg. of body weight), phentolamine (Regitine,® 10 mg. per kg.) or prednisolone (Hydeltrasol,® 20 mg. per kg.) were used. Metaraminol was administered by continuous intravenous infusion to maintain mean arterial pressure at a level 20 mm. less than the control value before the onset of shock, and treatment was continued for a period of two hours. Two animals were studied in each experiment. A coin was flipped to determine by chance which animal would be treated, the other animal serving as a simultaneous untreated control.

The vasopressor agent increased slightly the period of survival as well as the number of survivors. The adrenergic blocking agent and sympatholytic drug decreased the survival rate. Combined use of

TABLE 1.—*The Effect of Therapy on Fatality Time and Survival Following Production of Shock With Endotoxin in Dogs*

	Number		Endotoxin mg./kg. of Body Weight	Mean Fatality Time (Hours)		Survivors		Statistical Significance
	Treated	Untreated		Treated	Untreated	Treated	Untreated	
Metaraminol	9	9	3.6	13.6	10.9	0	0	.....
Prednisolone	9	9	6.6	13.0	6.6	3	2	p=.02
Prednisolone and metaraminol	9	9	3.5	25.1	14.1	4	2	p=.01
Dibenzyline	5	5	4.2	4.8	11.1	0	0	p=.05
Phentolamine	5	5	3.1	6.8	8.5	1	2	.....
Control	....	8	None	....	....	....	8	.....

vasopressor agents and corticosteroids provided the best survival data (Table 1). The usual severe reduction of urine output was prevented and the fall in pH of blood, which is due to accumulation of lactic acid and other acid metabolites during shock, also was considerably reduced.

It was concluded from these experiments that in dogs, although *pretreatment* with adrenergic blocking drugs may protect against the lethal effects of endotoxin, the adrenergic blocking agent and sympatholytic drugs are not necessarily beneficial if given after onset of shock. On the other hand, judicious use of a vasopressor amine, especially in conjunction with a corticosteroid hormone, may promote reversal of the state of shock and favor survival.[10]

COMMENT

The hazards of the therapeutic use of vasoconstrictor drugs have been emphasized by observers who believe that elevation in blood pressure is of little aid if it is brought about by vasoconstriction alone. Increased arterial pressure favors the flow of blood to coronary and cerebral vascular beds and may produce symptomatic improvement; the supply to other tissues, however, may be disproportionately decreased and the overall effect may be only transiently beneficial.

No direct clinical implication should be made from our experimental observations in dogs. There is no evidence that the hemodynamic disturbances that account for shock in dogs are similar to those occurring in man. However, these studies are significant in that they do not support conclusions based on other studies with dogs in which the dogs were treated *before* the onset of shock. Pretreatment with vasopressor agents was detrimental and sympatholytic drugs were beneficial. When treatment was begun *after* the onset of endotoxin shock, however, the sympatholytic drug decreased survival, and judicious use of vasopressor agent was clearly not detrimental.

We have also demonstrated in studies in patients, not reported here, that the sympathomimetic drugs increase cardiac output in bacterial shock. Beneficial effects may not be primarily due to vasoconstriction, but rather a consequence of increased blood flow, possibly produced by constriction of venous pools.[9]

It is also well known that these drugs exert a favorable influence on the heart itself. Drugs like norepinephrine and metaraminol increase myocardial contractility. Such a cardiotonic effect takes place independently of any beneficial action resulting from increased pressure in the coronary artery.[7] In patients in whom a cardiogenic factor accounts for progression of shock, which may be the case in most instances of protracted shock, this is an additional therapeutic consideration.

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